TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS WITH NEPHROPATHY BY MEANS OF CHLORAMBUCIL

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16. Abstract

Presents a review of American and foreign research results with the drug chlorobrucil in the treatment of kidney disease, as well as the side effects.

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TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS WITH NEPHROPATHY BY MEANS OF CHLORAMBUCIL*

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It is beginning to be accepted that drugs able to modify the immune response can also control the clinical characteristics of systemic lupus erythematosus in a high proportion of patients and, therefore, improve the course of those with affected kidneys. In 1970 Cameron et al. reviewed the use of such drugs in the treatment of lupus nephritis and concluded that cyclophosphamide has some advantages over other recommended drugs, especially azthioprine. Other authors have endorsed both the use of cyclophosphamide and azathioprine, but there is a not inconsiderable risk involved of medullary suppression and, in the case of cyclophosphamide, of alopecia and hemorrhaging cystitis. In a recent paper, Snaith et al. consider chlorambucil advantageous because of the relative absence of side effects and report on a group of six systemic lupus erythematosus patients treated with this drug. In the case of five of the female patients, the decision to use it came after failure of corticosteroids to control the progression of the renal illness within acceptable toxicity limits. The renal function improved after chlorambucil was started and the patients were doing well after six, five, three and two and one half years, respectively. Renal biopsies had shown that five of the patients suffered from focal proliferative glomerulonephritis and in two of the case, repeated biopsies showed quantitative improvement. The sixth patient was treated with chlorambucil when

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** Numbers in the margin indicate pagination of the original foreign text.

corticosteroids failed to control peripheral vascular lesions and hemolysis; the patient is still well after four years. They assume that the amenorrhea that developed in four of the patients was probably related to the chlorambucil treatment, but no other important side effects were observed, although one of the patients developed a certain degree of medullary depression during the treatment. In their judgement chlorambucil offers advantages over other immunosuppressors usually recommended in this case -- such as azathioprine and cyclophosphamide -- and believe that it causes a less severe medullary suppression; furthermore and as opposed to cyclophosphamide, it is not associated with alopecia and hemorrhaging cystitis.

They point out that in the majority of lupus patients there is no need to consider a cytotoxic therapeutic, since corticosteroids can control the disease symptoms at doses sufficiently low to prevent significant side effects. As Estes and Christian point out, even in subjects with affected kidneys the prognosis is not always bad, with an overall five-year survival rate of between 50 and 70 percent of patients whose biopsies had shown focal glomerulonephritis. As we have seen, four out of the five patients mentioned in the current paper fall within this category /474 and therefore the possibility of spontaneous improvement can not be ruled out.

The standard of illness in two of these cases was that of a subacute disease for various years prior to culmination in nephritis. In neither case did the renal function improve by administration of prednisolone by itself, but in both cases remission occurred after chlorambucil was administered. This functional improvement was evident from the changes observed in sequential renal biopsies; it was more evident in tubular and interstitial alterations in which a much higher volume of interstitial tissue was observed in the initial biopsy than on later occasions. In 1963 Harvey et

al. attributed both the tubular lesion and the increase in interstitial tissue to the presence of an advanced disease. The edema probably explains most of the increase in interstitial tissue and this viewpoint is supported by the significant reduction in this component, as seen from the second and later biopsies. The changes observed in the glomeruli and vessels are much less dramatic in nature and the focal glomerular lesion can not be doubted even in the last biopsies.

In another case it was noted that the combination of prednisolone and azathioprine led to a certain degree of improvement but satisfactory control of the renal manifestations of the disease was established only with the introduction of chlorambucil even though recently the continued presence of L.E. [Lupus erythematosus] cells proves that the basic illness has not yet been completely eliminated. In another case the renal function became worse during the four weeks following birth, and did not improve until chlorambucil was administered.

In another case the renal function worsened progressively until chlorambucil was introduced into the therapy, after which improvement was clearly observed. Later a certain degree of medullary suppression was observed, facilitating the development of a cytomegalovirus infection that could be related to immune response disruption, either directly because of chlorambucil, or as a part of the basic disease. In this last case, hemolysis was controlled only by prednisolone doses high enough to produce intolerable side effects; but after introducing chlorambucil, both hemolysis and vascular manifestations could be controlled with daily doses of only 10 mg prednisolone; the patient continued well.

In 1970 Cameron et al. concluded from their experiments that cyclophosphamide had advantages over azathioprine and that

proper clinical tests should be performed. A year later, Steinberg et al. found, in a double-blind comparison of cyclophosphamide and a placebo in patients with lupus nephritis, that cyclophosphamide was marginally superior; both clinical and laboratory criteria were followed. But their observations were carried out only over a short period of time, and no long range results on their patients were published.

In the case of cyclophosphamide, hemorrhaging cystitis and alopecia are not infrequent complications; the latter is especially unfortunate, as most of the patients are young women. From that point of view, Snaith et al.'s experience with chlorambucil -- not only for lupus, but also for other connective tissue processes -- is encouraging. They have found no non-hematological side effects and leukopenia and reductions in thrombocyte level never reached alarming proportions. As we already mentioned, in four of his six patients, chlorambucil treatment was accompanied by amenorrhea and one patient developed symptoms that suggested onset of menopause at the age of thirty four. In another patient amenorrhea preceded chlorambucil treatment by about six years; it was thought this reflected the seriousness of the basic disease. It has been recently shown that cyclophosphamide treatment can lead to testicular fibrosis and sterility in the male, and amenorrhea and ovary dysfunction in the female. In this regard there seems to be no advantage of chlorambucil over cyclophosphamide, but the information available is incomplete.

One important aspect is the risk of inducing tumors in patients treated extensively with cytotoxics, and some chromosome aberrations have been reported in patients treated with azathioprine. In this respect, Snaith et al., in preliminary investigations, were able to show that lymphocytes in 5 out of 10 patients treated with cyclophosphamide showed chromosome lesions; this compares with none out of 10 patients treated with

chlorambucil, but the significance of these findings is not yet certain and further investigations are indicated.

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